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(71) Applicant *(for all designated States except US)*: **CIPLA LTD.** [IN/IN]; 289, Bellasis Road, Mumbai Central, Mumbai 400 008 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LULLA, Amar** [IN/IN]; 289, Bellasis Road, Mumbai Central, Mumbai 400 008 (IN). **MALHOTRA, Geena** [IN/IN]; 289, Bellasis Road, Mumbai Central, Mumbai 400 008 (IN). **BUGTANI, Chiloo** [IN/IN]; 289, Bellasis Road, Mumbai Central, Mumbai 400 008 (IN).

(74) Agents: **BOAZ, Rani** et al.; Krishna & Saurastri, 74/F, Venus, Worli Sea Face, Mumbai 400 018 (IN).

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(54) Title: A PHARMACEUTICAL COMPOSITION CONTAINING BISPHOSPHONIC ACID(S) OR SALT(S) THEREOF AND A PROCESS OF PREPARING THEREOF

(57) Abstract: The pharmaceutical composition containing bisphosphonic acid(s) or salt(s) thereof, such as, alendronate sodium trihydrate, etidronate, clodronate, pamidronate or ibandronate, is for use in treatment of osteoporosis, and a preparation of the same, by providing a core having a bisphosphonic acid or salt thereof in or on the core, applying a seal coating around the core and applying an enteric coating around the seal coating.

TITLE OF INVENTION

A PHARMACEUTICAL COMPOSITION CONTAINING BISPHOSPHONIC ACID(S) OR SALT(S) THEREOF AND A PROCESS OF PREPARING THEREOF

FIELD OF INVENTION

PHARMACEUTICAL DRUG

The present invention relates to a pharmaceutical composition, and to a process of preparation thereof, and more particularly to a pharmaceutical composition containing bisphosphonic acid(s) or salts(s) thereof, which composition will be used for the treatment of osteoporosis.

The present pharmaceutical composition comprises by weight, about 5-40% by weight of an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutelidene-1, 1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1,bisphosphonic acid;

3-amino-1-hydroxypropylidene-1, 1-bisphosphonic acid;

3-(N,N-dimethylamino>-1-hyroxypropylidene-1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and

4-<hydroxymethylene-1,1-bisphosphonic acid)-piperidine.

In the present invention the preferred bisphosphonic acid is 4-amino-1-hydroxybutlidene-1, 1-bisphosphonic acid, i.e., alendronic acid; more preferable is its monosodium salt trihydrate, viz., alendronate sodium trihydrate, or other bisphosphonic acid(s) or salts(s) thereof, viz., etidronate, clodronate, pamidronate or ibandronate.

Method of preparation pf bisphosphonic acids may be found in e.g., U.S.Pat. No.3,962,432; U.S.Pat.No.4,954,598; U.S.Pat.No.4267,108; U.S. Pat. No.4,327,039; U.S.Pat.No.4,407,761; U.S.Pat.No.4,621,077;

U.S. Pat. No.4,624,947; U.S.Pat.No.4,746,654; U.S.Pat.No.4,922,077; and EPO Patent Pub.No.0,252,504 In particular, methods for preparation of 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid and 4-amino-1-hydroxy-butylidene-1; 1-bisphosphonic acid monosodium salt trihydrate may be found in U.S.Pat. No.4,407,761 and U.S.Pat.No.4,922,077 respectively.

The disadvantages of all the above inventions are that the compositions release the active almost instantaneously causing oesophageal discomfort and ulceritis due to the release of the active in the upper Gastro Intestinal Tract (GIT). The medication has to be taken on arising for the day atleast 30 minutes before the first food, beverages or medication of the day with a full glass (200ml) of plain water only. The patients are advised to sit upright for about 30 minutes after ingestion of medication and until their first food of the day. Patients are not allowed to take medication at bedtime or before arising on the day.

According to the present invention, there is provided a pharmaceutical composition for oral administration substantially comprising a core having bisphosphonic acids and salts thereof, coated with an acid resistant coat thereby releasing the active only in the alkaline environment of the lower GIT.

The purpose of the enteric coating employed in the present invention is to resist the acidic environment of the stomach, thus avoiding oesophaeal irritation. Accordingly, the disadvantage of the prescribed method of taking the medication, as explained above, can be overcome by the present invention.

The core containing of bisphosphonic acid(s) or salt(s) thereof, can be coated with a hydrophilic polymer known in the art (seal coating) Example Hydroxy Proply Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), Polyvinyl Pyrrolidone (PVP), Shellac, cellulose gums, xanthan gums, thereupon being coated with the enteric polymer.

A wide variety of conventional enteric coatings may be employed in the present invention, including for example: cellulose acetate phthalate, Hydroxy propyl methyl cellulose phthalate (HPMCP); hydroxypropyl cellulose acetyl succinate; polyvinyl acetate phthalate; copolymerised methacrylic acid/methacrylic acid methyl esters, such as Eudragit L 12.5, Eudragit L 100 55 or Eudragit S 100; and mixtures thereof. The enteric coating may contain conventional plasticisers, pigments and/or dispersants, including for example polyethylene glycols, triacetin, triethyl citrate, and Citroflex, dibutyl sebacate.

The enteric coating can be applied in any suitable manner, for example in the form of an aqueous dispersion in water, or other dispersing medium, or in the form of a solution. It is preferred that a dispersion or solution of the enteric coating is treated with an alkali in order to neutralise at least part of any free acid content. The alkali may be for example, a carbonate or hydroxide of sodium, potassium, magnesium or calcium.

Pharmaceutical compositions according to the present invention may comprise one or more additives. Examples of particularly useful additives include a diluent to aid dissolution of the pharmaceutically active ingredient, and a lubricant to aid flow of the active ingredient during manufacture. The

diluent may be, for example, lactose. The lubricant may be, for example, magnesium streate and/or talcum. It will be appreciated that the pharmaceutical compositions of the invention may contain any one or more other additives conventionally used in the formulation of pharmaceutical compositions. The excipients known in the art of manufacturing these dosage forms include lactose, microcrystalline cellulose, dicalcium phosphate, starch, sugar, disintegrants such as starch and derivatives of starch, sodium carboxy methyl cellulose and it's derivatives, crospovidone, etc.

The pharmaceutical composition as per the present invention may take the form of, tablets or peltabs or pellets in a capsule.

According to a first embodiment of the present invention, the bisphosphonic acid or salt thereof is present in the core. Suitably, the core of the pharmaceutical composition comprises a plurality of compressed granules of the bisphosphonic acid. This embodiment is particularly useful when it is desired to provide the pharmaceutical composition in tablets form, and there is further provided by the present invention a tablet which comprises pharmaceutical composition substantially as herein described, wherein the inert core is formed from a plurality of granules comprising the bisphosphonic acid, which granules are compressed together to form the core. According to the first embodiment of the present invention, the seal is applied around the active core, then the enteric coating is suitably provided around the seal coated active core.

According to a second embodiment of the present invention, the bisphosphonic acid or salt thereof is present in the active core. This embodiment of the invention is particularly applicable for the inclusion of a plurality of pellets in a capsule. The active cores of the pellets may typically be non-pareils and suitably provided in the form of sugar beads or sugar/starch beads. When the pellets comprise bisphosphonic acid or salt thereof loaded onto a plurality of inert cores suitable for inclusion in a capsule, the bisphosphonic acid can be supplied as a spray. For example, the bisphosphonic acid or salt thereof may be mixed with one or more additives before being loaded on the inert cores. As described above, the additives may include, for example, a solubiliser and/or a lubricant. The inert cores can be loaded with the bisphosphonic acid (together with any additives), and sprayed with a binder, in a centrifugal coating apparatus.

According to another embodiment of the invention, the seal coating is applied around the active core of each of the pellets to be provided in a capsule, and the enteric coating is suitably provided around the seal coating on each of the active cores. According to this embodiment of the invention there is therefore, provided a capsule which comprises a capsule shell containing a plurality of pellets.

According to another embodiment of the invention, bisphosphonic acid or salt thereof is present in the active core. This embodiment of the invention is particularly applicable for the compression of a plurality of pellets in a

tablet form. The active cores of the pellets may typically be non-pareils and suitably provided in the form of sugar beads or sugar/starch beads.

According to another embodiment of the invention, the seal coating is applied around the active core of each of the pellets, and the enteric coating is suitably provided around the seal coating on each of the active cores. These plurality of pellets together with conventional excipients such as disintegrants and binders are compressed into tablets, generally known as peltabs.

The following general and specific examples illustrate the invention. In each case, the active drug is bisphosphonic acid or salt thereof, unless indicated otherwise. Whilst sucrose (sugar) is the illustrated binding agent, other binding agents such as polyvinylpyrrolidone, shellac or xanthan gum, may be used instead.

General Examples:

Example 1:

A plurality of particles containing the active drug are prepared from the following materials:

Non-pareil seeds	95.00mg.
Active drug	13.03mg.
Sucrose	31.97mg.
Corn starch	32.00mg.
Talcum	10.00mg.
HPMC	1.00mg.
	183.00mg.

Water: as required:

Seal coating:

HPMC	7.2mg.
Talc	1.4mg.
Propylene glycol	1.4 mg.
	10.00mg.

Water: as required.

Isopropyl alcohol: as required.

Enteric coating:

Eudrajit L 100-55	22.50mg.
Sodium hydroxide	0.320mg.
Triethyl citrate	2.270mg
Talc	22.50mg.
Titanium dioxide	2.18mg.
Aerosil	0.23mg.
	50.00mg.

Water: as required

Initially, the active drug, the sucrose, the corn starch and the talcum are blended thoroughly to yield a dusting powder. The non-pareil seeds are loaded into a centrifugal coating apparatus, and then coated with the dusting powder while spraying the HPMC (hydroxypropyl methyl cellulose) solution, which results in the production of a plurality of discrete particles containing the active ingredients. The particles so obtained are dried using conventional tray dryers/fluid bed dryers to an outlet temperature of 45°C. These particles are then seal coated using HPMC solution and further enteric coated in suitable Wurster coating apparatus.

Example 2

Pellets:

A plurality of particles containing the active drug are prepared as follows:

Non-pareil seeds	95.00mg.
Active drug	13.03mg.
Sucrose	31.97mg.
Corn starch	32.00mg.
Talcum	10.00mg
HPMC	1.00mg
	183.00mg.

Water: as required:

Seal coating:

HPMC	7.2mg.
Talc	1.4mg.
Propylene glycol	1.4 mg.
	10.00mg

Water: as required.

Isopropyl alcohol: as required.

Enteric coating:

Eudrajit L 100-55	18.00mg.
Sodium hydroxide	0.25mg.
Triethyl citrate	1.81mg
Talc	18.00mg.
Titanium dioxide	1.75mg.
Aerosil	0.19mg.
	40.00mg.

Water: as required

Initially, the active drug, the sucrose, the corn starch and the talcum are blended thoroughly to yield a dusting powder. The non-pareil seeds are loaded into a centrifugal coating apparatus, and then coated with the dusting powder while spraying the HPMC solution, which results in the production of a plurality of discrete particles containing the active ingredients. The particles so obtained are dried using conventional tray dryers/fluid bed dryers to an outlet temperature of 45°C. These particles are then seal coated using HPMC solution and further enteric coated in suitable Wurster coating apparatus.

Example 3

Peltabs:

A plurality of a particles containing the active drug are prepared from the following materials:

Non-pareil seeds	110.07mg.
Active drug	13.03mg.
Sucrose	35.90mg.
Corn starch	21.00 mg.
Talcum	02.00mg
HPC-l Klucel	01.00mg
	183.00mg.

Water: as required:

Seal coating:

HPMC	7.2mg.
Talc	1.4mg.
Propylene glycol	1.4 mg.
	10.00mg.

Water: as required.

Isopropyl alcohol: as required.

Enteric coating:

Eudrajit L 100-55	22.50mg.
Sodium hydroxide	0.320mg.
Triethyl citrate	2.270mg
Talc	22.50mg.
Titanium dioxide	2.18mg.
Aerosil	0.23mg.
	50.00mg.

Water: as required

Microcrystalline cellulose	50.00mg
Croscarmellose sodium	7.00mg
	57.00mg.

Initially, the active drug, the sucrose, the corn starch and the talcum are blended thoroughly to yield a dusting powder. The non-pareil seeds are loaded into a centrifugal coating apparatus, and then coated with the dusting powder while spraying the HPC-L Klucel (hydroxypropyl cellulose) solution, which results in the production of a plurality of discrete particles containing the active ingredient. The particles so obtained are dried using conventional tray dryers/fluid bed dryers to an outlet temperature of 45°C. These particles are then seal coated using HPMC solution and further enteric coated in suitable Wurster coating apparatus, and is then suitably diluted with binders and disintegrants, and compressed by conventional means.

Specific examples:

Example 4

Tablets :

Tablet cores containing an active drug are prepared from the following materials:

Alendronate sodium trihydrate	13.03 mg.
Lactose	127.97mg.
Microcrystalline Cellulose (MCC)	103.00mg.
Croscarmellose Sodium	3.00mg.
Magnesium stearate	3.00mg
	250.00 mg

Seal coating:

HPMC	5.76mg.
Talc	1.12mg.
Propylene glycol	1.12 mg.
	8.00mg

Enteric coating:

Eudrajit L 100-55	6.750mg.
Sodium hydroxide	0.095mg.
Triethyl citrate	0.680mg
Talc	6.750mg.
Titanium dioxide	0.655mg.
Aerosil	0.070mg.
	15.00 mg.

Water: as required

Initially, the active drug is blended with the MCC, lactose and croscarmellose sodium in a suitable mixer. The blend containing the active drug is lubricated with magnesium stearate. Finally, the blend is compressed into a suitable shape for a tablet core using conventional compression equipment. The resulting tablet core is then coated using HPMC solution. These seal coated tablets are then enteric coated.

Example 5

Tablets

Tablet cores containing an active drug are prepared from the following materials:

Alendronate sodium trihydrate	13.03 mg.
Lactose	138.97mg.
Microcrystalline Cellulose (MCC)	90.00mg.
Croscarmellose	5.00mg.
Magnesium sterate	3.00mg
	250.00 mg

Seal coating:

HPMC	7.20mg.
Talc	1.40mg.
Propylene glycol	1.40 mg.
	10.00mg.

Enteric coating:

Eudrajit L 100-55	4.500mg.
Sodium hydroxide	0.064mg.
Triethyl citrate	0.455mg
Talc	4.500mg.
Titanium dioxide	0.436mg.
Aerosil	0.045mg.
	10.00mg.

Water: as required

Initially, the active drug is blended with the MCC, lactose and croscarmellose sodium in a suitable mixer. The blend containing the active drug is lubricated with magnesium stearate. Finally, the blend is compressed into a suitable shape for a tablet core using conventional compression equipment.

The resulting tablet core is then coated using HPMC solution. These seal coated tablets are then enteric coated.

We Claim:

1. A pharmaceutical composition containing bisphosphonic acid(s) or salt(s) thereof, such as, alendronate sodium trihydrate, etidronate, clodronate, pamidronate or ibandronate, for use in treatment of osteoporosis.

2. A process for preparing a pharmaceutical composition as claimed in claim 1, comprising of the steps of providing a core having a bisphosphonic acid or salt thereof in or on the core, applying a seal coating around the said core and applying an enteric coating around the said seal coating, the said seal coating comprising of at least one binding agent, and the said seal coating being selected from the group consisting of a sugar, polyvinyl-pyrrolidone, shellac and xanthan gum, HPMC, HPC, and the binding agent comprising a sugar.

3. A process as claimed in claim 2 wherein, the said bisphosphonic acids and salts thereof are selected from the group consisting of:
4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid;
N-methyl-4-amino-1-hydroxybutelidene-1, 1-bisphosphonic acid;
4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1,bisphosphonic acid;
3-amino-1-hydroxypropylidene-1, 1-bisphosphonic acid;
3-(N,N-dimethylamino>-1-hyroxypropylidene-1-bisphosphonic acid;
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid; and
4-<hydroxymethylene-1,1-bisphosphonic acid)-piperidine.

4. A process as claimed in claims 2 and 3, wherein the said composition releases the active only in the alkaline environment of the lower GIT, thus, resisting the acidic environment of the stomach, and thereby avoiding oesophageal irritation, and thus overcoming the disadvantages of the prescribed method of taking the medication.

5. A process as claimed in claims 2 to 3, wherein the said pharmaceutical preparation is in the form of tablets or pellets in capsule or peltabs.

INTERNATIONAL SEARCH REPORT

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PCT/IN 99/00060

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/663 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 421 921 A (CIBA GEIGY AG) 10 April 1991 (1991-04-10) page 2, line 38 -page 2, line 45 page 3, line 14 -page 3, line 18 page 3, line 36 -page 3, line 38 page 3, line 52 -page 4, line 7 page 5, line 52 -page 5, line 57 ---	1-5
X	WO 95 08331 A (MERCK FROSST CANADA INC ;BECHARD SIMON R (CA)) 30 March 1995 (1995-03-30) page 1, line 5 -page 1, line 19 page 3, line 14 -page 3, line 27 page 5, line 1 -page 5, line 3 page 6, line 23 -page 6, line 25 page 9, line 22 -page 9, line 26 --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Internatio...l Application No
PCT/IN 99/00060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 09995 A (TOMER RON ;TOMER ZEVULUN (IL); UNIPHARM LTD (IL)) 4 March 1999 (1999-03-04) page 1, paragraph 2 page 3, paragraph 7 -page 4, paragraph 1 claim 22	1-5
X	WO 93 09785 A (PROCTER & GAMBLE PHARMA) 27 May 1993 (1993-05-27) page 1, line 5 -page 1, line 18 page 2, line 4 -page 2, line 6 page 21, line 32 -page 23, line 11	1-5
A	WO 98 52564 A (WAIN CHRISTOPHER PAUL ;HAMIED YUSUF KHWAJA (IN); CIPLA LIMITED (IN) 26 November 1998 (1998-11-26) page 3, paragraph 1	1-5
A	WO 99 48498 A (HENRIKSEN KRISTIAN LUND ;SOERENSEN KAREN EICHSTEDT (DK); KANN HELL) 30 September 1999 (1999-09-30) page 9, line 35 -page 10, line 10	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic.. Application No
PCT/IN 99/00060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0421921 A	10-04-1991	AT 104856 T	15-05-1994
		AU 623036 B	30-04-1992
		AU 6228390 A	14-03-1991
		CA 2024631 A	08-03-1991
		DD 298049 A	06-02-1992
		DE 59005517 D	01-06-1994
		DK 421921 T	30-05-1994
		ES 2052228 T	01-07-1994
		FI 93169 B	30-11-1994
		HU 59008 A,B	28-04-1992
		IE 63668 B	31-05-1995
		IL 95558 A	31-08-1995
		JP 3009713 B	14-02-2000
		JP 3099016 A	24-04-1991
		MX 22254 A	01-12-1993
		NO 176646 B	30-01-1995
		NZ 235187 A	26-03-1992
		PH 27186 A	16-04-1993
		PT 95209 A,B	22-05-1991
		US 5096717 A	17-03-1992
		ZA 9007100 A	29-05-1991
WO 9508331 A	30-03-1995	US 5431920 A	11-07-1995
		AU 681700 B	04-09-1997
		AU 7735794 A	10-04-1995
		CA 2170537 A	30-03-1995
		EP 0720480 A	10-07-1996
		JP 9504276 T	28-04-1997
WO 9909995 A	04-03-1999	AU 8819598 A	16-03-1999
		EP 0996452 A	03-05-2000
		ZA 9807538 A	23-02-1999
WO 9309785 A	27-05-1993	AU 661080 B	13-07-1995
		AU 3060492 A	15-06-1993
		BR 9206797 A	31-10-1995
		CA 2122479 A,C	27-05-1993
		CZ 9401230 A	16-11-1994
		EP 0613373 A	07-09-1994
		FI 942366 A	20-05-1994
		HU 67681 A	28-04-1995
		JP 7501073 T	02-02-1995
		NO 941894 A	19-07-1994
		NZ 245214 A	28-05-1999
		PT 101085 A,B	28-02-1994
		RU 2120798 C	27-10-1998
		SK 59594 A	08-03-1995
		US 5622721 A	22-04-1997
		US 5935602 A	10-08-1999
WO 9852564 A	26-11-1998	AU 7539098 A	11-12-1998
		EP 0983067 A	08-03-2000
		GB 2343117 A	03-05-2000
		ZA 9804266 A	20-01-1999
WO 9948498 A	30-09-1999	AU 2714899 A	18-10-1999